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Evaluating the Safety and effectivenesS in adult KorEaN patients treated with Tolvaptan for management of autosomal domInAnt poLycystic kidney disease (ESSENTIAL): final report

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Objectives : Tolvaptan, a selective vasopressin V2 receptor antagonist, was first approved by Korean FDA in 2015 as a treatment option in autosomal dominant polycystic kidney disease (ADPKD). In order to prescribe Tolvaptan safely and effectively, we designed the phase 4 clinical trial among Korean ADPKD patients with chronic kidney disease (CKD) stage 1-3.
Methods : A total of 117 Korean patients aged 19 to 50 with rapidly progressing ADPKD were enrolled in the study. The patients were prescribed Tolvaptan for 24 months with the maximum tolerable dose up to 120mg per day. The primary outcome was the incidence of treatment emergent adverse events (TEAEs) including hepatic adverse events. The secondary outcomes were the annual mean percent change of total kidney volume (TKV) and the annual mean change of estimated glomerular filtration rate (eGFR).
Results : A total of 489 TEAEs occurred in 106 (90.6%) patients. A total of 17 cases (14.5%) of hepatic adverse events occurred during the study period and mostly within the first 18-month period. However, liver enzymes were normalized after drug discontinuation. Although it was not statistically significant, patients with a previous history of liver disease as well as those with mild elevation of liver enzyme showed higher frequency of hepatic adverse events. Comparing with the predicted value from calculation, Tolvaptan attenuated both TKV growth and eGFR decline rate.
Conclusions : Although the incidence of hepatic adverse events was higher in Korean ADPKD patients compared to the previous studies, Tolvaptan can be prescribed safely and effectively using meticulous titration and 1-month interval monitoring.

Figure 1. ESSENTIAL trial.png

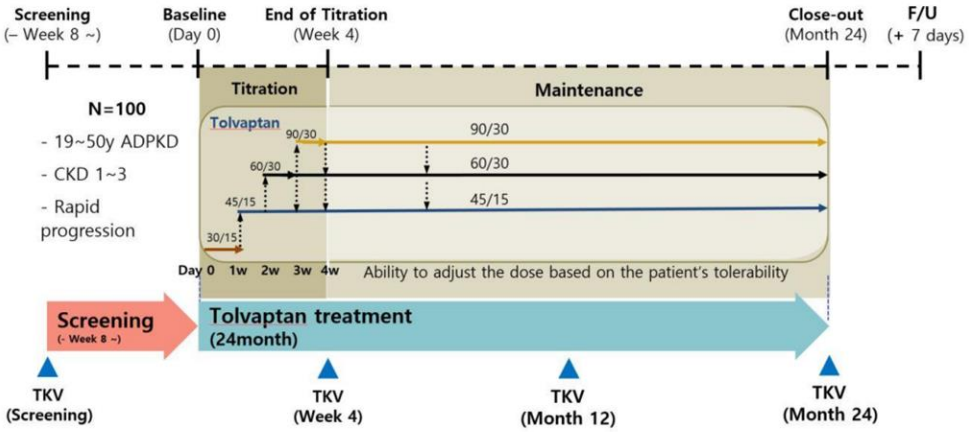

Figure 1. ESSENTIAL trial.png

Trial	ESSENTIAL	TEMPO 3:4		REPRISE	
Study duration	2 years	3 years		1 year	
Monitoring interval	1-month interval until 18 months, 3-month interval thereafter	Every 4 months		Every month	
Subjects	Tolvaptan (n=117)	Tolvaptan (n=958)	Placebo (n=484)	Tolvaptan (n=681)	Placebo (n=685)
ALT > 3xULN	15 (12.8%)	42 (4.4%)	5 (1.0%)	38 (5.6%)	8 (1.2%)
ALT or AST > 3xULN or TB > 2xULN	17 (14.5%)	48 (5.0%)	11 (2.3%)	41 (6.0%)	8 (1.2%)
ALT or AST > 3xULN & TB > 2xULN	1 (0.85%)	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)
ALT or AST > 3xULN & TB > 2xULN & ALP < 2xULN	1 (0.85%)	2 (0.2%)	0 (0%)	0 (0%)	0 (0%)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; ULN, upper limit of normal.